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UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ALABAMA
SOUTHERN DIVISION

SHAMEKA M. BRIDGES and PETERSON BRIDGES,	)	
Plaintiffs,	)	
v.	)	**CASE NO. 2:14-cv-00036-VEH**
BAYER HEALTHCARE PHARMACEUTICALS, INC., BAYER PHARMA AG, and BAYER OY,	)	
Defendants.	)	

DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION TO EXCLUDE THE OPINIONS OF DENA R. HIXON, M.D. AND DAVID W. FEIGAL JR, M.D.

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INTRODUCTION

Unable to attack the qualifications of Bayer's regulatory experts — Drs. Hixon and Feigal combined have dozens of years of relevant experience at the Food and Drug Administration ("FDA") — Plaintiffs instead offer scattered criticisms that are unsupported by law or reason. Some arguments are plainly absurd: Plaintiffs claim that the experts should be excluded for not reviewing hundreds of thousands of pages of irrelevant documents or because they cannot recall from rote memory the most minute details of studies they cite. Others are grossly misguided, including Plaintiffs' assertion that experts must evaluate medical literature despite that literature's inability to offer insight on relevant issues (the Friedman articles), and their insistence that all experts must engage in the so-called Bradford-Hill causation assessment, regardless of the FDA's own standards. Plaintiffs also argue against facts and reason. They allege that Drs. Hixon and Feigal will present FDA "state of mind" testimony but are unable to identify any such testimony in their reports or depositions. They complain that Bayer will present duplicative testimony from both Drs. Hixon and Feigal, despite numerous assurances to the contrary. Finally, they assert that Dr. Hixon's testimony in this case should be severely constrained based on findings in a separate case involving different issues. These nitpicking criticisms come nowhere close to justifying the sweeping exclusion Plaintiffs seek.

FACTUAL BACKGROUND

Dr. Dena Hixon is a licensed physician with nearly 13 years of experience as a Medical Officer at the FDA, including work in the Office of New Drugs, Division of Reproductive and Urologic Drug Products. Pls.' Br. Ex. A, Hixon Report 1. In this role, Dr. Hixon repeatedly reviewed Investigational New Drug ("IND") applications, New Drug Applications ("NDA"), postmarketing labeling proposals, safety reports, and supplemental applications for new drug uses or changes in drug labeling. *Id.* Faced with this experience, Plaintiffs are forced to concede Dr. Hixon's ample basis for offering her opinions: "She certainly possesses the regulatory qualifications to do so . . . ." Pls.' Br. 12.

Dr. David Feigal is a licensed physician with 12 years of experience in various positions at the FDA, including 5 years at the FDA's Center for Drug Evaluation and Research ("CDER") in Director- and Acting Director-level positions. Pls.' Br. Ex. B, Feigal Report 1–2. His responsibilities similarly included review and approval of product labeling, evaluating updated safety warnings, and assessing and providing initial approval for new medications. *Id*. at 2. Plaintiffs cannot and do not challenge his qualifications: at the FDA, he served several levels above Plaintiffs' proffered regulatory expert. Ex. 1, Ross Dep. 40:2–9.

In this matter, both experts wrote lengthy reports systematically addressing Mirena's regulatory history, including Bayer's consideration of the potential risk of IIH with Mirena use. They describe Mirena's labeling and opine that Bayer acted reasonably with respect to its evaluation of IIH in light of the available scientific evidence and the population using Mirena, including the fact that women who receive Mirena are at an especially high risk for the development of IIH. The experts meticulously supported their reports with citations to the extensive regulatory record they reviewed in formulating their opinions.

LEGAL STANDARD

Under Rule 702, *Daubert*, and its progeny, expert testimony must be (1) reliable, (2) relevant and able to assist the jury, and (3) proffered by a qualified expert. Fed. R. Evid. 702; *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 589–95 (1993); *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 147–52 (1999). Experts are "qualified" if they possess "knowledge, skill, experience, training, or education" regarding the topics of their testimony. Fed. R. Evid. 702. To be reliable, expert testimony must be based on "sufficient facts or data" and must be "the product of reliable principles and methods" that have been "reliably applied" to the particular "facts of the case." Fed. R. Evid. 702; *see also Adams v. Lab. Corp. of Am.*, 760 F.3d 1322, 1327 (11th Cir. 2014). In its gatekeeping function, the Court's goal "is to ensure that an expert 'employs in the courtroom the same

level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Adams*, 760 F.3d at 1327 (quoting *Kumho Tire*, 526 U.S. at 152).

ARGUMENT

In place of offering a coherent, global challenge to Bayer's regulatory experts, Plaintiffs offer scattershot criticisms that justify neither exclusion nor limitations on the relevant testimony.

I. Drs. Hixon and Feigal Offer Reliable Opinions Based on Sufficient Facts and Data

A. *Daubert* Does Not Require Experts to Review Hundreds of Thousands of Pages of Documents and Depositions

Plaintiffs offer blustery indignation over Dr. Hixon's decision not to review each of the nearly one million pages produced from Mirena's IND/NDA. Pls.' Br. 13 ("According to counsel's latest count, approximately 481,000 pages have been produced under the MIR_INDNDA_label and another 326,796 under the MIR_INDNDA-R_label. ***Yet, Hixon never reviewed the entire file. Not even close."*** (emphasis added)). Under this proposed standard, no expert report could ever be issued. Even at the blistering pace of one page per minute, reviewing a relatively modest 807,000-page IND/NDA would take approximately 6.5 years, working 40 hours per week, 52 weeks per year. *Daubert* and Rule 702 are not so draconian. Instead, they require that expert opinions be grounded in "sufficient facts or data." Fed. R. Evid. 702(b).

In place of reviewing pages of data irrelevant to her opinions, Dr. Hixon used her extensive regulatory experience to appropriately identify and review the relevant information. Plaintiffs neither challenge Dr. Hixon's qualifications to do so, *see*, *e.g.*, Pls.' Br. 12 (conceding that Dr. Hixon "***certainly possesses the regulatory qualifications***" to "review the [IND and NDA] for Mirena" (emphasis added)), nor offer any evidence or authority demonstrating that Dr. Hixon chose to review the "wrong" data.

As Dr. Hixon explained when she was challenged on this point, she applied just the kind of focused review in this case that FDA reviewers employ:

> DR. HIXON: I mean, all the raw data is analyzed in the study reports and it's reviewed at FDA and the information is summarized by the disciplines that are relevant to each section of the NDA.
>
> . . . A team leader would look at the reviews of -- the summary reviews of each individual discipline and go into any sections of the NDA that they needed to look at in order to reach their conclusion.
>
> Likewise, with the kind of task that I had before me here, that same sort of thing was the relevant information that needed to be reviewed, not to dig out every animal study, every piece of raw data from anything, but to get the overall big picture and look at the sections that are relevant to the question at hand.

Pls.' Br. Ex. C, Hixon Dep. 29:2–21. Dr. Hixon employed her regulatory expertise to determine which materials were *not* relevant to her inquiry, such as "hundreds of thousands of pages of chemistry, manufacturing, and controls information." *Id*. at

25:5–7. By employing the same approach to her expert work that an FDA team leader uses when evaluating a new medication for approval, Dr. Hixon exercised "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Adams*, 760 F.3d at 1327 (quoting *Kumho Tire*, 526 U.S. at 152).[1]

The same reasoning also dooms Plaintiffs' tag-along criticism of both Drs. Hixon and Feigal for not recalling which depositions they read in full, versus depositions from which they read "key sections." Pls.' Br. 5, 17–18. There is no basis for arguing that an expert may be excluded for not reading every page of testimony, particularly in the absence of ***any*** showing that the expert failed to review anything material. *See* Fed. R. Evid. 702 (expert testimony must be based on "sufficient facts or data").

B. *Daubert* Does Not Require Experts to Memorize Details from Studies Cited in Their Reports

Plaintiffs further highlight the flimsiness of their *Daubert* challenge by criticizing Dr. Hixon for not committing to rote memory minute details from studies cited in her report. Pls.' Br. 6–7 (criticizing Dr. Hixon for not recalling details such as "the number of participants in the studies" and "the response

[1] There is some irony to this criticism, given that Plaintiffs own regulatory experts do not purport to have conducted such an extensive review — indeed, Dr. Fraunfelder spent a grand total of ten hours in reviewing materials and writing his report. Dr. Hixon reviewed not only all of the materials purportedly relied upon by Drs. Ross and Fraunfelder, but also more than 200 additional documents.

rates"). Plaintiffs do not and cannot argue that Dr. Hixon failed to provide support for key opinions about IIH incidence rates and risk factors in her heavily-footnoted report, and they offer no authority for their argument that a failure to recall details from studies requires exclusion under *Daubert*.[2]

Memorization of minute details is not a metric for the reliability or helpfulness of an expert's opinion, nor should it be. Any "lapses in memory are traditionally challenged through cross-examination and do not render [expert] opinion testimony unreliable." *Pension Comm. of Univ. of Montreal Pension Plan v. Banc of Am. Sec., LLC*, 716 F. Supp. 2d 220, 227 n.45 (S.D.N.Y. 2010).

C. Dr. Hixon's Regulatory Role Includes Review of IIH Data and Risk Factors

Plaintiffs' criticism of Dr. Hixon's memory is embedded within a claim that she steps beyond her regulatory role when testifying as to IIH incidence rates and risk factors. Pls.' Br. 6. This criticism demonstrates a fundamental misunderstanding of the regulatory expert's role. One of Dr. Hixon's major tasks in this litigation is to assess the adequacy of Mirena's IIH labeling. No expert can analyze the adequacy of Mirena's IIH labeling without developing some

[2] In addition to being irrelevant, Plaintiffs' criticism of Dr. Hixon's memory is inaccurate and unfair. Dr. Hixon recalled significant details about certain studies and engaged in extensive questioning with counsel on issues of study designs and findings. *See, e.g.*, Pls.' Br. Ex. C, Hixon Dep. 80:13–82:21 (discussing the Durcan study). Counsel also repeatedly refused Dr. Hixon's request for copies of studies to refresh her recollection. *See id*. at 80:25–81:2, 87:19–88:3.

understanding of the disease, its incidence rate, and its relevant risk factors. Indeed, understanding the underlying epidemiology of the disease and related risk factors constitutes an essential aspect of evaluating whether a potential risk should appear in a medicine's label. *See* Center for Drug Evaluation & Research, FDA, *Guidance for Industry: Good Pharmacovigilance Practices* 15 (2005), , *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf ("To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics)."). As Dr. Hixon explained in her deposition, FDA regulators consider this type of data throughout the regulatory process:

> I do have some expertise in those fields [epidemiology and pharmacokinetics] just by virtue of the kind of work I did at FDA that incorporated those kinds of data into the regulation process.

Pls.' Br. Ex. C, Hixon Dep. 75:23–76:13.

By considering the same types of data FDA regulators consider when making approval decisions, Dr. Hixon has approached her expert work with the same degree of intellectual rigor employed by experts in her field. *Adams*, 760 F.3d at 1327 (reversing the trial court's exclusion of an expert after finding the

expert had employed an established diagnostic system commonly used by others in her field).

D. *Daubert* Does Not Require Experts to Review a Particular Article When They Have Considered the Relevant Underlying Data

Plaintiffs criticize Drs. Hixon and Feigal for not citing a small number of review publications by Dr. Deborah Friedman that list levonorgestrel, the synthetic hormone used in Mirena, among other substances that may be "associated" with IIH. *See* Pls.' Br. 7–8, 18. But it is meritless to claim that an expert opining on a potential relationship between a medication and an event must cite every article that makes even a passing reference to a potential *association* between the substance and the relevant condition. This conclusion is plain from the briefest review of Dr. Friedman's passing references to levonorgestrel. Dr. Friedman's articles — none of which reports original research — refer only to a potential "association" between levonorgestrel and IIH. The articles do not even discuss Mirena; instead, they cite literature about Norplant, a different contraceptive system, and one that Drs. Hixon and Feigal expressly considered. *Compare* Pls.' Exs. G, H, I, K (Friedman publications each citing Norplant information), *with* Pls.' Br. Ex. A, Hixon Report 21–28 (discussing Norplant information), *and* Pls.' Br. Ex. B, Feigal Report 25–29 (same).

Drs. Hixon and Feigal fully considered the available evidence concerning Norplant and explained that Norplant's potential risks are not automatically attributable to Mirena. As discussed in the Hixon and Feigal reports, Norplant was implanted into women's arms and circulated levonorgestrel throughout their bloodstreams. Mirena also contains levonorgestrel, but in a significantly lower dose, which is delivered directly to the uterus, rather than circulating systemically. These differences affect the medications' risk profiles, and as Drs. Hixon and Feigal explain, evidence regarding Norplant and IIH is not relevant for assessing whether there is a causal relationship between Mirena and IIH. Pls.' Br. Ex. A, Hixon Report 21–28; Pls.' Br. Ex. B, Feigal Report 25–29. The reliability of their opinions is in no way undermined because they did not cite to an article that merely referenced the very potential association they fully considered.

E. *Daubert* Does Not Require Defense Regulatory Experts to Apply the Bradford-Hill Causation Analysis

Plaintiffs contend that Drs. Hixon and Feigal should be excluded for their decision not to engage in a "proper" analysis of the so-called Bradford-Hill causation factors.[3] Plaintiffs' criticism is inapposite for two reasons.

[3] The Bradford-Hill factors are one set of guidelines, comprising nine criteria, which epidemiologists may, under certain circumstances, consider when assessing whether a causal relationship exists between a putative cause and effect.

First, Plaintiffs have not demonstrated that the Bradford-Hill criteria are applicable to this case. As Bradford-Hill himself explained, the framework applies only after an "association between two variables" is "perfectly clear-cut and beyond what we would care to attribute to the play of chance." *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 678 (M.D.N.C. 2003) (citing Bradford Hill, *The Environment and Disease: Association or Causation*, 58 Proc. Royal Soc'y Med. 295, 295–300 (1965)); Pls.' Br. Ex. B, Feigal Report 48. After a rigorous assessment of the evidence, Drs. Hixon and Feigal determined that there was not a "perfectly clear-cut" association between Mirena and IIH, and thus made the reasoned decision not to engage in a Bradford-Hill assessment. *See* Pls.' Br. Ex. B, Feigal Report 24–50; Pls.' Br. Ex. A, Hixon Report 21–36. Plaintiffs may disagree with their conclusions, but that disagreement does not give rise to any legitimate *Daubert* challenge.[4] *Daubert*, 509 U.S. at 595 (the court focuses on experts' principles and methodology, "not on the conclusions that they generate").

Second, Plaintiffs make no showing that an expert must engage in a Bradford-Hill analysis to support a regulatory opinion. *See* Pls.' Br. Ex. C, Hixon Dep. 75:1–2) ("My role is purely as a regulatory expert, *not as a causation expert . . . .*" (emphasis added)). Tasked with assessing the adequacy of Mirena's

[4] Dr. Feigal elected to address Bradford-Hill as applied by one of Plaintiffs' witnesses, who has since been withdrawn. Pls.' Ex. B, Feigal Report 48–50.

labeling, both experts turn to FDA's *Guidance for Industry: Good Pharmacovigilance Practices*, which lists seven factors to consider when assessing the relationship between a medication and an adverse outcome. Pls.' Br. Ex. A, Hixon Report 29–30; Pls.' Br. Ex. B, Feigal Report 31–32. Drs. Hixon and Feigal properly applied these standards, and Plaintiffs do not argue otherwise (or even mention these standards).

II. Drs. Hixon and Feigal Do Not Offer "State of Mind" Testimony

Plaintiffs claim that Drs. Hixon and Feigal both "*attempt*" to offer opinions that "*suggest*" that the FDA would not approve an IIH warning on the Mirena label. Pls.' Br. 19. This accusation is simply not correct, as demonstrated by Plaintiffs' inability to cite support for this claim in either expert's report or deposition. In fact, neither Dr. Hixon nor Dr. Feigal offer any opinion regarding whether the FDA would approve an IIH warning.

III. Plaintiffs Are Not "Unfairly Prejudiced" by Dr. Hixon's Testimony

Plaintiffs make the footnote argument that Dr. Hixon's testimony should be limited due to certain restrictions she faced in the Mirena uterine perforation MDL.[5] In that litigation, Dr. Hixon was unable to disclose due to confidentiality concerns a few specific internal FDA conversations that directly related to the risk

[5] The plaintiffs in the Mirena MDL perforation litigation alleged that properly-inserted Mirenas spontaneously perforated through the uterus and into the abdominal cavity. Bayer secured summary judgment in the MDL after the plaintiffs' general causation experts were excluded under *Daubert*.

of perforation. Believing that the plaintiffs could be "unfairly prejudiced" because Dr. Hixon had "participated directly in some of the events at issue but [could not] discuss them," the MDL court carved out limited portions of her testimony. Pls.' Br. 11 n.2.

Plaintiffs have offered no justification for the same ruling here on the distinct IIH issue. Dr. Hixon's report and testimony make clear that she does not rely on "insider information" to support her positions. Each of her opinions is supported by either publically-available documents or materials produced in this litigation. At no point during her IIH deposition did Dr. Hixon refuse to answer counsel's questions, and Plaintiffs have taken no steps to develop a record of prejudice resulting from Dr. Hixon's testimony. In short, nothing in the record suggests that Dr. Hixon "could not fully disclose the bases of her opinions." Pls.' Br. 11 n.2. Plaintiffs should not be permitted to limit Dr. Hixon's testimony by piggybacking off an unrelated finding, made by another court in another case, involving testimonial limitations that are not at issue here.

IV. Bayer Will Not Present Duplicative Regulatory Testimony

Plaintiffs need not be concerned that Bayer will present duplicative regulatory testimony in this case. Trial is several months away, and Bayer has made it abundantly clear to Plaintiffs that at trial it will not offer improperly cumulative testimony. *See* Defendants' Opposition to Plaintiffs' Motion to

Exclude Proposed Testimony of Dr. Beau Bruce, Dr. Nancy Newman, and Dr. Robert Langer. Bayer will not call both Dr. Hixon and Dr. Feigal, and Plaintiffs offer no authority suggesting that now, at the *Daubert* stage, Bayer is obligated to select its trial witnesses.

CONCLUSION

For the foregoing reasons, Plaintiffs' motion should be denied.

Dated: September 15, 2016

Respectfully submitted,

/s/ Kathleen Paley

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CERTIFICATION

I hereby certify as an officer of the court that I have affirmatively and diligently sought to submit to the Court only those documents, factual allegations, and arguments that are material to the issues to be resolved in this motion, that careful consideration has been given to the contents of this submission to ensure that it does not include vague language, overly broad citations of evidence, or misstatements of law, and that this submission is non-frivolous in nature.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that on September 15, 2016, a copy of the foregoing was filed electronically via the Court's CM/ECF system, which will have sent notice to the following attorneys of record in this matter:

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